Pharmacokinetics of nicotine in healthy elderly people

Background: Mortality hazards of smoking extend well into later life; this suggests that smoking cessation will continue to improve life expectancy in older people. The pharmacology and pharmacokinetics of nicotine have not been studied in elderly subjects. Drug disposition and pharmacodynamic responsiveness to nicotine may change with age, and conclusions founded on data from studies of younger populations may not apply to elderly populations. Our aim was to assess the pharmacokinetics of nicotine in healthy elderly subjects compared with healthy adults.

Methods: Twenty healthy elderly subjects (age, 65-76 years) and 20 healthy adult subjects (age, 22-43 years) were given an intravenous infusion of 0.028 mg/kg of nicotine over 10 minutes. Nicotine and cotinine concentrations were measured in plasma and urine. Heart rate and blood pressure were monitored.

Results: For most adult and elderly subjects nicotine distributed according to a two-compartment system. Even though there was a large interindividual variation within and overlap between groups, nicotine total clearance (−23%), nonrenal clearance (−21%), renal clearance (−49%), volume of central compartment (−37%), volume of distribution at steady state (−17%), and cotinine renal clearance (−18%) were statistically significantly decreased in elderly subjects compared with adults. Maximal heart rate response to nicotine was decreased in the elderly subjects (−29%).

Conclusion: Even though statistically significant differences were observed, the disposition of nicotine does not seem to be changed to a clinically important extent in elderly subjects compared with younger adults. (Clin Pharmacol Ther 2001;69:57-65.)

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Strong evidence has been provided that continued smoking increases the risk of cardiovascular mortality and death from cancer at all ages, particularly from smoking-related cancers.[1-4] The findings indicate that the mortality hazards of smoking extend well into later life and suggest that cessation will continue to improve life expectancy in older people. One approach to help elderly smokers to stop smoking is the use of replacement therapy with nicotine. However, no pharmacodynamic or pharmacokinetic studies on nicotine have been performed exclusively on elderly subjects, and conclusions founded on studies of younger populations may not apply to elderly populations. The disposition and pharmacodynamic responsiveness to many drugs have been found to change with age.[5-7] General changes in absorption, distribution, and elimination of drugs appear to be consistent with known physiologic changes in the aging population[8-10] (eg, reduced lean body mass,[11,12] increased proportion of body fat,[13] reduced proportion of body water,[14] reduced liver mass[15] and liver blood flow,[15,16] and reduced glomerular filtration rate[17,18] and tubular function[19]). Age-related differences in the response to drugs, including adverse events, arise not only from pharmacokinetic but also from pharmacodynamic differences[20,21] and from impairment of homeostatic mechanisms.[22]

Nicotine is a high hepatic extraction drug.[23] About 80% of nicotine clearance is accounted for by metabolic clearance,[24] with oxidation of nicotine to cotinine as the quantitatively major metabolic pathway.[25] As a consequence of the age-related reduction of hepatic blood flow, a reduced nonrenal clearance of nicotine might be anticipated. The urinary excretion of unchanged nicotine during normal pH conditions is low,[26,27] and the decline in glomerular filtration rate and tubular function associated with old age will probably only have a

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Received for publication June 22, 2000; accepted Nov 29, 2000.

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0009-9236/2001/$35.00 + 0 13/1/113181
doi:10.1067/mcp.2001.113181

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marginal effect on nicotine total clearance. Changes in body composition might affect the volume of distribution because nicotine is primarily distributed in lean body tissue.[28] Therefore there are reasons to believe that several primary pharmacokinetic parameters of nicotine may be changed in an elderly population compared with a younger population.

The primary aim of this investigation was assessment of the pharmacokinetics of nicotine in healthy elderly subjects compared with younger healthy adults.

METHODS

Subjects

Twenty healthy elderly subjects (8 men and 12 women; age, 65-76 years) who were not taking any medication and 20 healthy adult subjects (10 men and 10 women; age, 22-43 years) were recruited for the study. Thirty-five subjects were smokers (>10 cigarettes per day), 4 were using wet snuff (>20 g/d), and 1 subject used both cigarettes and snuff. All of the subjects gave informed consent, and the study was approved by the ethics committee of Lund and was performed according to the Declaration of Helsinki.

Study design

The subjects were requested not to smoke or snuff or use any other form of nicotine-containing products for 36 hours, from 8:00 PM 2 days before dose administration until the last blood sample had been drawn 23 hours after dose administration. Compliance to the nonsmoking condition was confirmed by the performance of measurements of expired carbon monoxide in the morning of the day before administration, on the day of administration, and on the day after administration. Readings were recorded directly from a Bedfont Micro Smokerlyzer (Upchurch, Kent, England). Values of 15 ppm or more led to exclusion from the study. No coffee or tea drinking was allowed before and during the first 2 hours after drug administration. The subjects were requested to drink 200 mL of fluid every hour for the first 12 hours after drug administration. The subjects did not fast before drug administration.

Because of the chronopharmacokinetics of nicotine,[29] all of the subjects were started at the same clock time. At 8:00 AM, an intravenous solution of 0.28 mg/mL of nicotine was infused by a motor syringe over 10 minutes. The dose was 0.028 mg/kg of body weight.

Venous blood samples were taken in heparinised vacutainer tubes 20, 16, and 12 hours before drug administration; immediately before the dose; and 5, 10, 20, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 23 hours after the start of the infusion. The samples were centrifuged at 1500g for 10 minutes at 4°C, and the plasma was transferred to cryotubes and frozen (–20°C) within 30 minutes. Urine sampling was done 20 to 16, 16 to 12, and 12 to 0 hours before dose, and on the study day, urine sampling was performed 0 to 1, 1 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 23 hours after the start of the infusion. The volume and pH of the urine were measured (pH-meter). A 10 mL urine specimen of each urine collection was transferred to a urine tube and frozen (–20°C).

Heart rate and systolic and diastolic blood pressures were recorded in connection with blood sampling on the day of nicotine administration. Measurements were performed with the use of an automatic oscillometric measuring blood pressure device (N*IS; Levimed AB, Höganäs, Sweden).

Analysis of nicotine and cotinine

Nicotine and cotinine levels in plasma and urine were determined by capillary gas chromatography with the use of a nitrogen-sensitive detector after single-step liquid-liquid extraction of the plasma or urine sample.[30] The capillary chromatography system was multilevel calibrated at five points with three replicates in each point. Optimal curve fit was obtained by linear regression analysis. During the analyses, recalibration was performed after every 75th sample. The plasma samples were analyzed twice; however, if the results of nicotine differed more than 10% and the absolute difference was greater than 1.0 ng/mL, a third analysis was performed. The median value was used for pharmacokinetic calculations. The urine samples were analyzed once. The limit of quantitation (LOQ) was 0.5 ng/mL for nicotine and 3.8 ng/mL for cotinine.

Pharmacokinetic assessment

Nicotine plasma concentration data were analyzed with the Kinetica 2.0.1 software (Innaphase, Paris, France) with the use of compartmental and model-independent methods, and cotinine plasma data were analyzed with the use of model-independent methods. Individual plasma concentration data from each subject and the exact time points were used throughout analysis. Nicotine and cotinine plasma concentrations below the LOQ of 0.5 ng/mL and 3.8 ng/mL, respectively, at the terminal end of the plasma concentration-time curve were omitted from analysis. The pharmacokinetic parameters were calculated with the use of standard equations.[31] Correction for exponentially declining nicotine and cotinine baseline concentrations more than or equal to the LOQ was performed. Baseline concentrations below the LOQ were set to 0.

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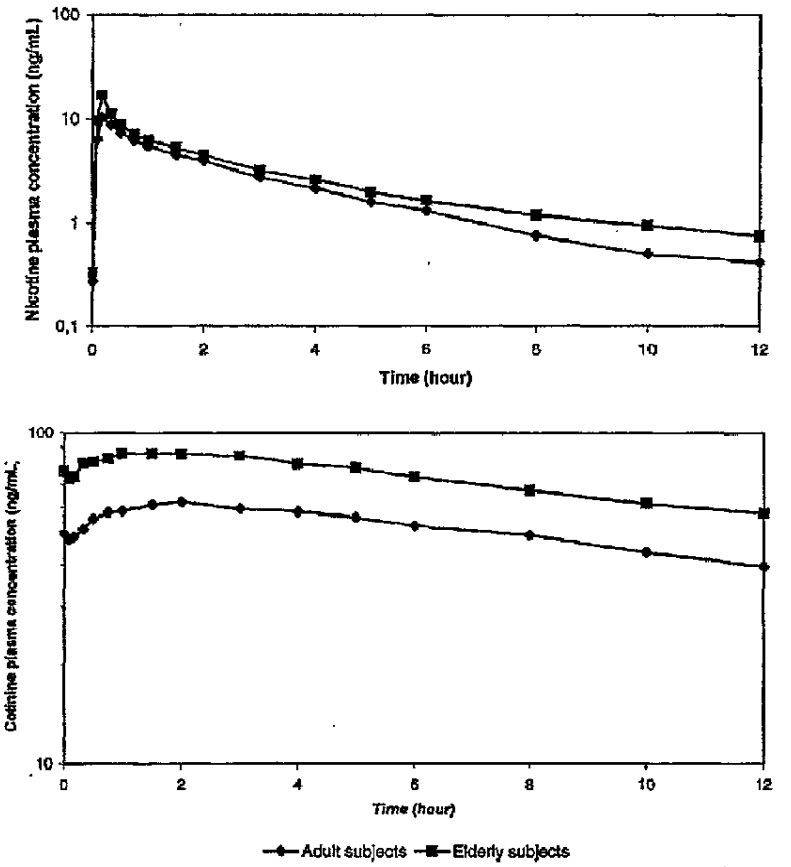

Fig 1. Nicotine and cotinine plasma concentration-time curves in healthy adult subjects and in healthy elderly subjects.

The area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated as the following:

$$AUC_{0-t} + calcClast/\lambda$$

in which t is the terminal time point with a plasma concentration more than or equal to the LOQ, AUC_{0-t} is the area under the plasma concentration-time curve for time 0-t, calcClast is the calculated concentration at time t, and λ is the terminal elimination rate constant. The AUC and area under the first moment curve were calculated by the trapezoidal rule with use of linear interpolation for ascending plasma concentrations and log-linear interpolation for descending concentrations. Renal clearance was calculated as the following:

$$Xu_{0-t}/AUC_{0-t}$$

in which Xu_{0-t} is the amount excreted in urine from 0 to time t and AUC_{0-t} is the area under the plasma concentration-time curve for time 0-t (not corrected for baseline concentration). Criteria used to discriminate between alternate polyexponential models comprised distribution of residuals, correlation between and precision of computed parameter estimates, and the F ratio test.[32] Terminal elimination rate constants were computed by linear regression of the log concentration ver-

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Table I. Nicotine pharmacokinetic parameters

Parameter	*P value (adults versus elderly subjects)*	*Adult subjects*			*Elderly subjects*		
		Mean ± SD	*Range*	*95% CI*	*Mean ± SD*	*Range*	*95% CI*
Total clearance(mL/min)	.0005	1307 ± 251	837-1900	1191-1426	1002 ± 240	638-1558	889-1114
Renal clearance (mL/min)	.033	63 ± 55	12-243	37-89	32 ± 23	5-81	21-43
Nonrenal clearance (mL/min)	.0019	1245 ± 259	817-1837	1124-1367	984 ± 239	605-1552	869-1099
V_c (L)	.0013	174 ± 50	83-258	149-200	109 ± 48	28-187	86-133
V_d (L)		347 ± 122	183-635	290-404	294 ± 78	168-501	257-330
V_{ss} (L)	.025	303 ± 80	183-480	266-341	250 ± 50	163-336	226-273
$t_{\frac{1}{2}}$ (h)		3.17 ± 1.43	1.88-8.37	2.50-3.83	3.52 ± 1.08	1.08-5.83	3.01-4.03
MRT (h)		3.96 ± 1.34	2.39-8.55	3.33-4.59	4.30 ± 1.01	2.86-5.90	3.83-4.77
$AUC_{0-\infty}$ (h · ng/mL)	.013	26.6 ± 5.7	15.3-35.1	23.9-29.2	33.1 ± 8.0	20.2-48.0	29.3-36.8
Sigma Xu(23 h) (μg)		106 ± 73	32-311	72-141	81 ± 50	18-182	57-105
Xu of dose (%)		5 ± 4	1-18	3.5-7.4	4 ± 3	1-10	3.0-5.6
Mean urine pH		6.6 ± 0.5	5.7-7.8	6.4-6.9	6.6 ± 0.4	5.9-7.5	6.4-6.8

SD, Standard deviation; CI, confidence interval; V_c, volume of central compartment; V_d, volume of distribution; V_{ss}, volume of distribution at steady state; $t_{\frac{1}{2}}$, elimination half-life; MRT, mean residence time; Xu, amount excreted in urine.

sus time curve in the terminal log-linear phase. Because daytime and nighttime total clearance differ,[29] data points at 23 hours were omitted from calculations of the terminal elimination rate constants. If these data points were included in the analysis unreasonably long terminal elimination half-lives would have been generated.

Statistical analysis

Data were tested for normality with the use of Shapiro-Wilk's test. Differences between healthy elderly subjects and healthy adults were tested with Student *t* test. If the assumption of normality was not fulfilled, the Wilcoxon rank sum test was used. The statistical package used was SAS 6.12 (SAS Institute, Inc, Cary, NC). Data are presented as mean values ± standard deviations.

RESULTS

Plasma concentrations of nicotine and cotinine

The mean plasma concentration versus time curves of nicotine and cotinine are shown in Fig 1. Baseline nicotine concentrations were similar for both study groups: 0.3 ± 0.3 ng/mL and 0.3 ± 0.5 ng/mL, respectively, for the adult subjects and the elderly subjects. Peak nicotine concentrations (not baseline corrected) achieved at the end of the intravenous infusions were 10.4 ± 3.4 ng/mL for the adults and 17.0 ± 8.0 ng/mL for the elderly subjects. The decrease of the nicotine plasma concentrations was somewhat slower for the elderly subjects compared with the adult subjects (Fig 1). Cotinine baseline concentrations and peak concentrations were 49.8 ± 26.1 ng/mL and 62.2 ± 23.9 ng/mL, respectively, for the adults and 76.4 ± 43.0 ng/mL and 86.7 ± 38.3 ng/mL, respectively, for the elderly subjects. The plasma concentrations decreased with the same rate in both study groups (Fig 1).

Nicotine pharmacokinetics

The pharmacokinetic parameters of nicotine after compartmental analysis are shown in Table I. There was a good agreement between data generated by noncompartmental analysis and by compartmental analysis. Nicotine parameters obtained by compartmental analysis that showed a statistically significant difference between adult and elderly subjects are shown in Fig 2. Only compartmental data, presented as mean values ± standard deviations, are given in the following sections.

Primary pharmacokinetic parameters. For most of the adult subjects (17), as well as for the elderly subjects (14), nicotine was distributed according to a two-compartment system. Individual total clearance values as a function of age are shown in Fig 2. Mean total clearance was decreased by approximately 25% in elderly subjects compared with adults ($P = .0005$; Table I). Also when normalized for body weight, the difference was statistically significant (19.3 ± 4.5 L/kg and 14.9 ± 4.1 L/kg; $P = .0002$). There was a considerable overlap between the two groups, and approximately 70% of the clearance values of the elderly subjects were contained within the minimum to maximum range of those of the adults (Fig 2). The mean renal clearance was decreased by approximately 50% in the elderly subjects compared with the adults ($P = .033$, Table I).

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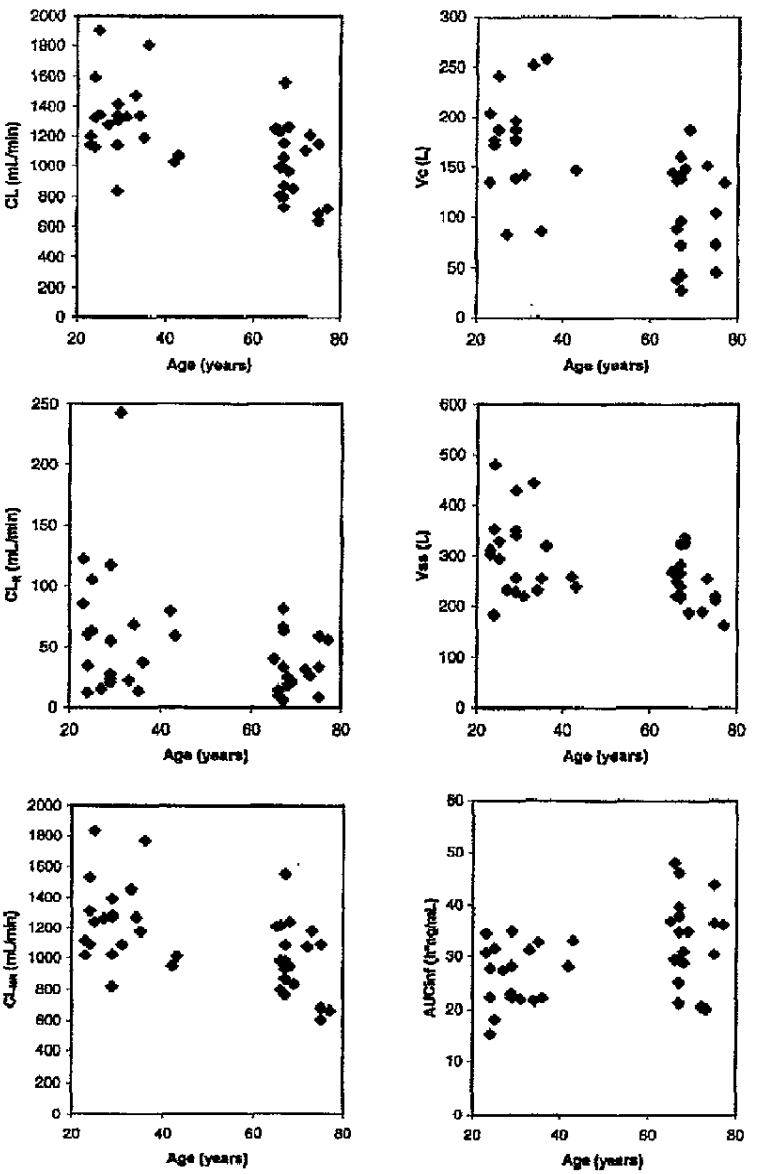

Fig 2. Nicotine pharmacokinetic parameters showing a statistically significant difference between adult and elderly subjects. CL, Total clearance; CL_R, renal clearance; CL_{NR}, nonrenal clearance; V_C, volume of central compartment; V_{SS}, volume of distribution at steady state; AUCinf, area under the plasma concentration-time curve extrapolated to infinity.

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Table II. Cotinine pharmacokinetic parameters

Parameter	*P value (adults versus elderly subjects)*	*Adult subjects*			*Elderly subjects*		
		Mean ± SD	*Range*	*95% CI*	*Mean ± SD*	*Range*	*95% CI*
C_{max} (ng/mL)		17.8 ± 4.4	8.7-24.0	15.7-19.9	19.4 ± 5.7	9.2-30.9	16.7-22.1
$t_{½}$ (h)		14.0 ± 4.8	7.4-24.2	11.8-16.2	15.1 ± 3.9	9.1-24.3	13.3-16.9
MRT (h)		21.5 ± 7.0	12.4-35.7	18.2-24.8	22.9 ± 5.6	14.2-35.9	20.3-25.6
$AUC_{0-\infty}$ (h · ng/mL)		414 ± 143	178-692	347-482	420 ± 122	222-697	363-477
Renal clearance (mL/min)	.0082	11 ± 3	6-18	10-13	9 ± 3	4-14	8-10

SD, Standard deviation; CI, confidence interval; C_{max}, maximum concentration; $t_{½}$, elimination half-life; MRT, ***.

One adult subject had a high renal clearance (243 mL/min). This subject had a low urinary pH (5.7), and 18% of the nicotine dose was excreted in the urine. In spite of the fairly large difference in mean values, most renal clearance values of the elderly subjects were contained within the minimum to maximum range of those for the adult subjects (Fig 2). The distribution of individual nonrenal clearance values was the same as found for total clearance (Fig 2); this showed a decreased nonrenal clearance of approximately 20% to 25% for elderly subjects compared with adult subjects. This difference was statistically significant ($P = .0019$). A plot of individual volume of central compartment values as a function of age is shown in Fig 2. There was a large interindividual variation in both groups. One third of the elderly subjects had volume of central compartment values below the range of those of the adults. The volume of the central compartment was statistically significantly decreased in the elderly subjects ($P = .0013$; Table I; Fig 2). The volumes of distribution were similar in the adult and elderly subjects, 347 ± 122 L (5.5 ± 2.4 L/kg) and 294 ± 78 L (5.0 ± 1.1 L/kg), respectively. The volume of distribution at steady state was lower in the elderly subjects compared with the adults (250 ± 50 L and 303 ± 80 L, respectively; $P = .025$; Table I). When normalized for body weight, the difference was less: 4.1 ± 0.8 L/kg in the elderly subjects and 4.5 ± 1.5 L/kg in adults; it was not statistically significant.

Secondary pharmacokinetic parameters. Because of the lower total clearance in elderly subjects (similar doses of 1.9 ± 0.4 mg for the elderly subjects and 2.0 ± 0.4 mg for the adults) the $AUC_{0-\infty}$ was statistically significantly increased ($P = .013$; Table I; Fig 2) in elderly subjects compared with adults (33.1 ± 8.0 ng · h/mL and 26.6 ± 5.7 ng · h/mL, respectively). The terminal elimination half-life and mean residence time were increased in the elderly subjects compared with the adults, but they were not statistically significantly increased (Table I).

Urinary data. The percentage of the dose that was excreted in urine did not differ between adult and elderly subjects (5% ± 4% and 4% ± 3%, respectively). The mean urinary pH was identical for the adult and elderly subjects (6.6 ± 0.5 and 6.6 ± 0.4, respectively).

Cotinine pharmacokinetics

The pharmacokinetic parameters after noncompartmental analysis are given in Table II. $AUC_{0-\infty}$, maximum concentration, elimination half-life, and mean residence time were similar both in magnitude and range for the adult and elderly subjects. Renal clearance was slightly but statistically significantly decreased in the elderly subjects compared with the adult subjects ($P = .0082$).

Hemodynamic effects

After the nicotine infusion there was an initial increase in heart rate and systolic and diastolic blood pressure; this increase reversed after approximately 30 minutes. Maximal heart rate increase was significantly ($P = .0062$) lower in elderly subjects than in adults (15 ± 6 bpm and 21 ± 8 bpm, respectively) even though the maximal nicotine plasma concentration was higher in the elderly subjects (16.8 ± 7.8 ng/mL) compared with the adults (10.4 ± 3.5 ng/mL). There were no differences between elderly and adult subjects in terms of blood pressure responses, both systolic and diastolic.

Adverse events

Of a total of 40 subjects in this study, 35 reported 68 adverse events (16 elderly and 19 adult subjects reported 31 and 37 adverse events, respectively). Almost all of the subjects (n = 35) noted symptoms such as pain, numbness, or tension localized to the arm in which the infusion was given. These local reactions started shortly after the start of infusion and subsided in the majority of subjects while the 10-minute infusion was still ongoing; in a few cases, the reactions subsided at the end of

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the infusion or shortly after the end of the infusion. Furthermore, there were 14 reports of dizziness or light headedness (6 elderly subjects and 8 adults), 4 reports of dry mouth or lips (3 elderly subjects and 1 adult), 3 reports of nausea (1 elderly subject and 2 adults), and singular reports of euphoria, cold hands and feet, palpitations, feeling of warmth, sweating, and paraesthesiae. These were all of short duration, and many abated before the infusion had ended. Of 68 adverse events, 40 were reported as mild (23 elderly subjects and 17 adults) and 27 as moderate (8 elderly subjects and 19 adults). One report of nausea was scored as severe. There were no serious or unexpected adverse events, withdrawals, or dropouts as a result of adverse events in this study.

DISCUSSION

Total clearance and nonrenal clearance were decreased by 25% and 20%, respectively, and renal clearance was decreased by 50%. About 80% of nicotine clearance is accounted for by metabolic clearance in the liver.[24] The lower nonrenal clearance indicates a reduced hepatic extraction of nicotine in the elderly subjects, most probably as a consequence of a reduced liver blood flow.[15,16] Liver size (volume and mass),[15] and thus intrinsic clearance, also decreases with age, but the effect on nicotine clearance is likely to be minor.

Normal aging is associated with reduction of renal function. Glomerular filtration rate[17,18] and tubular function[19] gradually decline with age. A renal function test of the two populations used in this study showed lower glomerular filtration rate (iohexol clearance) in the elderly subjects compared with the adults (87 ± 19 mL/min and 116 ± 16 mL/min [mean ± standard deviation], respectively). The mean volume of urine voided during the day and night after nicotine administration was 2.4 L for the adults and 1.8 L for the elderly subjects, with no difference in urine pH between the two groups (pH = 6.6). Renal excretion of nicotine is influenced by pH[26,27] and rate of urine flow[26]; a low pH and a high urine flow promote the excretion of unchanged nicotine by decreasing tubular reabsorption. The lower nicotine renal clearance in the elderly (–50%) may thus be explained by the decreased glomerular filtration rate (–25%) and lower urine flow (–25%) in this group. However, a change in renal function will only have a limited effect on nicotine disposition because nicotine renal clearance only constitutes about 5% of total clearance.

A decrease in lean body mass and total body water and an increase in body fat comprise changes in body composition associated with old age. Nicotine is primarily distributed in lean body tissue, and the decrease in volume of distribution at steady state (–15%) observed in the elderly subjects is of the same order of magnitude as the age-related decrease in lean body mass.[11,12] A pronounced effect of age was noted for the volume of the central compartment, which was decreased by about 40% in the elderly subjects. As a result, a higher mean maximum concentration value was found in this group compared with the adult subjects (16.8 ng/mL and 10.4 ng/mL, respectively). The reason for the decrease of volume of the central compartment is not clear, but it may be caused by the age-related decrease in lean tissue mass. Calculations of volume of the central compartment in this study were based on venous plasma concentrations, which reflect the concentration of drug in arterial blood minus the amount extracted during the passage through the body tissues. A decreased lean body mass may have resulted in less nicotine extracted and therefore higher initial venous blood concentrations in the elderly subjects. Similar volumes of the central compartment may have been obtained if arterial concentrations had been used in the calculations.[33,34] Drug distribution is also affected by binding to plasma proteins. However, the fraction of nicotine bound to protein is low,[24] and a change in plasma protein content should have negligible effects on nicotine disposition.

The pharmacokinetics of cotinine do not seem to be significantly different in elderly subjects compared with adults. Maximum concentration and $AUC_{0-\infty}$, both corrected for cotinine baseline concentrations, elimination half-life, and mean residence time, were very similar for the two groups. Cotinine renal clearance was decreased by about 20% in the elderly subjects, which was of the same magnitude as the decreased glomerular filtration rate in this age group. This will have only a marginal effect on the total clearance of cotinine because cotinine renal clearance is about 20% of total clearance.[35] However, higher baseline cotinine concentrations were observed in the elderly subjects. Without data on primary plasma pharmacokinetic variables, no firm conclusion about the cause of this finding may be drawn. On the basis of an analysis of transdermal nicotine users, Gourlay and Benowitz[36] concluded that there was no change in steady-state cotinine plasma levels or estimated plasma clearance values in individuals who were 18 to 69 years old and who were using patches with the same nicotine content. Cotinine plasma levels are primarily determined by nicotine dose,[37] and in view of the similarities between the age groups in terms of the secondary pharmacokinetic variables, the higher baseline levels in the elderly subjects may be the result of higher prestudy nicotine intake in this group. On the basis of findings of diminished urinary excretion of

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cotinine in relation to nicotine-N-oxide in elderly smokers compared with younger smokers, an age-related change of nicotine metabolism by means of alternative oxidative processes has been suggested.[38]

This study did not show any major differences between healthy adults and elderly healthy subjects in cardiovascular responsiveness to nicotine. Baseline pulse rates were similar in the two groups, whereas systolic and diastolic blood pressure were slightly higher in the elderly subjects compared with the adults (139/81 mm Hg and 124/78 mm Hg, respectively).

The initial chronotropic effect of nicotine is probably not mediated by adrenomedullary release of epinephrine but rather by sympathetic neuronal release of norepinephrine in the myocardium.[39] Nicotine increased heart rate somewhat less in the elderly subjects (~15 bpm) than in the adults (~21 bpm) without any differences in systolic and diastolic blood pressure changes between the two groups. The higher nicotine plasma levels achieved at the end of the infusion in the elderly subjects (a mean of 16.8 ng/mL compared with a mean of 10.4 ng/mL in the adults) suggests that cardiovascular reactivity to nicotine was decreased in the elderly subjects. This is in accordance with previous findings that have shown an age-related decrease in cardiac β-adrenergic responsiveness both in vitro[40] and in vivo.[41] It should be appreciated, however, that it is the arterial concentration that best represents the concentration that determines pharmacodynamic effects. As discussed, the higher venous concentrations in the elderly subjects may have been caused by less tissue extraction of the arterial nicotine content. The arterial concentrations may therefore have been similar in the two groups.

CONCLUSION

The disposition of nicotine did not seem to be changed to a clinically important extent in elderly subjects compared with younger adults, even though statistically significant differences were observed.

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PM3006723297

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